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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/392,682	09/09/1999	DEITER C. GRUENERT	480.18-4	1612

7590 12/14/2001

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EXAMINER

LOEB, BRONWEN

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 12/14/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/392,682

Applicant(s)

GRUENERT ET AL.

Examiner

Bronwen M. Loeb

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 December 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: 17-44.

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
10. ☒ Other: see attached sheets


REMY YUCEL, PH.D
PRIMARY EXAMINER

Continuation of 3. Applicant's reply has overcome the following rejection(s): The rejections under 35 USC §112, second paragraph have been withdrawn in light of Applicant's amendments.

Attachment to PTO-303

CONTINUATION OF BOX 10:

Applicant has argued that the specification is enabling for gene therapy and that the rejection under 35 USC§112, first paragraph should be withdrawn. Applicant is reminded that a disclosure must be enabled at the time of filing. See MPEP §2164.01. Applicant's argument has been considered in full and is not deemed persuasive. Applicant first states that gene therapy is not per se an unpredictable art. This statement is correct in that one cannot predict success for gene therapy methods given the current state of the art, and this is more certainly true at the time of the claimed effective filing date for the instant application. Phase I clinical trials, used to evaluate safety, determine a safe dosage range, and identify side effects for a method or drug, typically enrolls 20-80 patients. Therefore, two or three patients having some success in over 300 clinical trials is an 0.05% "success" rate and clearly predicts a lack of success for gene therapy methods. Applicant cites Ferber (Exhibit B) as further evidence that one of skill in the art has a reasonable expectation of success using Applicant's method for gene therapy. The Examiner disagrees. Ferber, published in 2001, characterizes Applicant's method as a technique which "offer[s] a *potential* means to achieve a longtime dream of gene therapy.." (p.1639 box; emphasis added). Indeed, Ferber starts the article with the statement that most nonviral delivery methods "have not been as efficient as viruses in shuttling genes into cells" (p. 1638) and the concluding paragraph of the article states "complex nonviral carriers are a long way from the clinic, but they may offer a glimpse of future gene therapies" (p. 1642). Therefore, one of skill in the art would recognize only that Applicant's method is considered promising, not that it would be successful.

Applicant states that they have met the legal standard for enablement. Applicant argues that "replacing target gene fragments in even a small percentage of instances" would enable the method. This statement is not correct. While the claims do not explicitly recite a method of gene therapy, the specification does and it is the only use taught for the in vivo method. Gene therapy implies a therapeutic effect. Thus, what needs to be demonstrated for enablement is that the claimed method would achieve a therapeutic effect. Applicant points out the working examples using the method to replace genetic sequences in cell cultures and states that "the Office Action presents no reasoning or evidence to question that these successful modifications demonstrated in vitro are not predictive of successful in vivo modification". One of skill in the art is well aware that in vitro work cannot be extrapolated to in vivo work. For instance, Applicant's own article (Exhibit C), published in 2001, states that "one difficulty in going from in vitro to in vivo experiments is that the conditions relevant to transfer (the delivery vehicle, the target and the route of delivery) are different". (pp.961-962 bridge)

Applicant concludes the argument rebutting the enablement rejections by presenting five post-filing date articles. Only two of these articles present in vivo work, Exhibit C and Exhibit E. These articles were published in 2001 and 1998 respectively. Applicant states that these article demonstrate successful in vivo use of the claimed method following the teachings of the specification. The specification generally teaches the use of liposomes as one method for in vivo work. Example 19 is a prophetic in vivo example and refers to Example 17 for the preparation of the replacement DNA fragment and example 15 for the encapsulation. Example 17 does not discuss the preparation of a DNA fragment at all. Example 15 uses DOPE and gramicidin S to prepare liposomes. In contrast, Exhibit C uses four different carriers, none of which consists of DOPE and gramicidin S. Exhibit E uses Lipofectin, which consists of DOTMA. Given that efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy, the delivery vehicle used is critical. None of the three delivery vehicles used in Exhibit C, nor the

Art Unit: 1636

vehicle used in Exhibit E, were taught or suggested in the instant specification. Thus, these articles do not serve to show the specification was enabled as filed for in vivo methods. The enablement rejection is extended to new claims 41-44.

The amendments filed do not serve to overcome the art rejections. With regard to Berns, Berns et al teaches targeting exons for replacement by homologous recombination. See col. 9, lines 64-67. Berns also teaches that the targeting DNA may be constructed exclusively from genomic DNA (col. 11, lines 62-63) or synthetically (col. 12, lines 39-42). Such methods would not include vector sequence. The rejection over Berns is extended to new claims 41-44.

With regard to Vega, Applicant argues that their claims exclude foreign genes. The claims as written do not exclude foreign genes; the method's intent is to replace a target fragment; the limitation recited for the replacement DNA fragment does not exclude a foreign gene since it could be located between two replacement fragments and the intent of the method would be achieved. If no foreign gene may be included, this should be recited in the claim. With regard to Vega, the replacement DNA consists of a "fragment of DNA without sequence foreign to the target locus, containing the correct version of the mutation at the locus as the only source of non-homology" (p. 246, column bridge). Vega therefore does not teach the use of vector sequences in the replacement DNA. Vega also teaches the same gene. The rejection over Vega is extended to new claims 41-44.

With regard to Kay, while Kay et al propagate their replacement DNA sequence in a vector, all of the plasmid sequence is removed by restriction enzyme digestion prior to carrying out the method of target replacement. See col.12, lines 50-52. Thus, Kay et al does not teach vector sequence and still anticipates the claims. The size of the fragment used is not relevant as the claims do not recite a size limitation. The rejection over Kay is extended to new claims 41-44.

With regard to Tsui, Applicant is reminded that the intended use is given no patentable weight. Thus, although Tsui does not teach using their PCR-generated fragments of the cystic fibrosis gene, these fragments do have all the limitations recited in claim 37 (contrary to Applicant's assertion) and thus anticipates claim 37. See Figures 18 (drawing sheets 30-43), 19 and pp. 64-65.

It is noted that Applicant has not rebutted the rejection over Shesely et al.

None of the rejections under 35 USC §102 or 35 USC §103 are withdrawn.